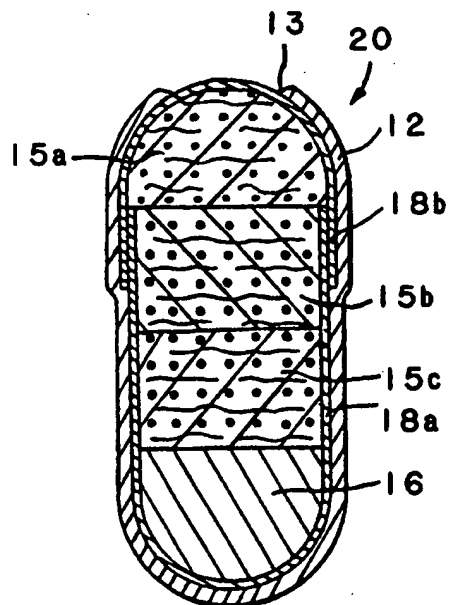




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/00, 9/20	A1	(11) International Publication Number: WO 95/06460 (43) International Publication Date: 9 March 1995 (09.03.95)
(21) International Application Number: PCT/US94/09709 (22) International Filing Date: 31 August 1994 (31.08.94) (30) Priority Data: 08/114,573 31 August 1993 (31.08.93) US (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors: DONG, Liang, C.; 457 Sierra Vista, Unit 5, Mountain View, CA 94043 (US). ESPINAL, Steven, D.; 226 Acalanes Drive, Sunnyvale, CA 94086 (US). WONG, Patrick, S.-L.; 2030 Cornell Street, Palo Alto, CA 94306 (US). GUTTARD, George, V.; 22434 St. Andrews Avenue, Cupertino, CA 95014 (US). HAMEL, Lawrence, G.; 1215 Arbor Court, Mountain View, CA 94040 (US). (74) Agent: SABATINE, Paul, L.; Alza Corporation, 950 Page Mill Road, (P.O. Box 10950), Palo Alto, CA 94303-0802 (US).		(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: DISPENSER CONTAINING HYDROPHOBIC AGENT (57) Abstract <p>The present invention is directed to a formulation for the delivery of hydrophobic active agents to a fluid environment of use while avoiding aggregation of the hydrophobic agents in the environment, the formulation comprising a hydrophobic active agent in an amount of 50 wt% (percent by weight) or greater together with polyoxyethylene 40 stearate and a disintegrant. The present invention is also directed to an improvement in a fluid-activated delivery device (10) wherein the delivery device includes a housing (12) defining an internal compartment (14), an active agent formulation (15) in the compartment, exit means (13) in the housing (12) for delivering the active agent formulation (15) from the delivery device, a fluid-activated expandable driving member (16) in the compartment, optionally a partition layer between the active agent formulation (15) and the driving member (16), and optionally a lubricant subcoat (18); wherein the improvement comprises an active agent formulation (15) comprising a hydrophobic active agent in an amount of 50 wt% (percent by weight) or greater together with polyoxyethylene 40 stearate and a disintegrant.</p>		



BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LV	Latvia	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MD	Republic of Moldova	TJ	Tajikistan
DE	Germany	MG	Madagascar	TT	Trinidad and Tobago
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain	MN	Mongolia	US	United States of America
FI	Finland			UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

DISPENSER CONTAINING HYDROPHOBIC AGENT

FIELD OF THE INVENTION

The present invention pertains to the delivery of an active agent to an animal. More particularly, the invention is concerned with the controlled administration of a hydrophobic active agent, preferably a drug, to an animal
5 over time, where the delivery device has a high loading of the hydrophobic agent.

BACKGROUND OF THE INVENTION

Osmotic delivery devices for administering an active agent to a biological fluid environment of use are known in the art. Examples of such
10 devices are disclosed in, e.g., U.S. Pat. Nos. 4,627,850; 4,663,148; 4,663,149; 4,678,467; 4,692,326; 4,716,031; 4,814,180; 4,874,388; 5,023,088; and 5,126,142. While the prior art delivery devices usually work successfully for their intended purpose, the present inventors have observed that the devices often do not function well when the dispensed formulation
15 contains a hydrophobic active agent in a very high loading, of 50% or greater. It has been found that when a formulation containing at least 50% hydrophobic agent is dispensed from the previous devices, the agent aggregates in the device when it is exposed to the fluid biological environment of use during release. Such agent aggregation is often the
20 cause of uncontrolled and nonuniform release of the agent, and this in turn results in erratic release profiles and system malfunction.

While devices having a low loading of drug (of up to 40% or, more normally, less) can solve the problem of agent aggregation, this low loading creates a problem in those instances where it is desired to deliver a large

amount of agent from the device. The amount of active agent necessary to be included in such a device would require a very large amount of formulation at a low dosing, making the device far too large and bulky to be useful as a practical matter as an implant or an oral dosage form, for
5 example.

In the light of the above presentation, it will be appreciated by those versed in the dispensing art to which this invention pertains that a pressing need exists for a dosage form that can deliver a hydrophobic active agent to a biological environment of use in large amounts in a small volume while
10 overcoming erratic delivery release profiles and system malfunction.

SUMMARY OF THE INVENTION

The present invention is directed to a formulation for the delivery of hydrophobic active agents to a fluid environment of use while avoiding aggregation of the hydrophobic agents in the environment, the formulation
15 comprising a hydrophobic active agent in an amount of 50 wt% (percent by weight) or greater, polyoxyethylene 40 stearate, and a disintegrant.

The present invention is also directed to an improvement in a fluid-activated delivery device wherein the delivery device includes a housing defining an internal compartment, an active agent formulation in the
20 compartment, exit means in the housing for delivering the active agent formulation from the delivery device, a fluid-activated expandable driving member in the compartment; optionally a partition layer between the active agent formulation and the driving member, and optionally a lubricant subcoat; wherein the improvement comprises an active agent formulation
25 comprising a hydrophobic active agent in an amount of 50 wt% or greater, polyoxyethylene 40 stearate, and a disintegrant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates one embodiment of a device according to the present invention.

FIG. 2 illustrates another embodiment of a device according to the present invention.

FIGS. 3A and 3B are bar graphs showing the release rate profile of a gemfibrozil drug formulation of the present invention (FIG. 3A) and of a prior art gemfibrozil formulation (FIG. 3B).

FIGS. 4A, 4B, 4C, and 4D are bar graphs showing the release rate profile of a gemfibrozil drug formulation of the present invention (FIG. 4A), and of gemfibrozil formulations that do not fall under the present invention (FIGS. 4B, 4C, and 4D).

FIGS. 5A and 5B are bar graphs showing the release rate profile of a gemfibrozil drug formulation of the present invention (FIG. 5A), and of a gemfibrozil formulation that does not fall under the present invention (FIG. 5B).

FIG. 6 is a bar graph showing the release rate profile of a phenytoin drug formulation of the present invention.

FIG. 7 is a bar graph showing the release rate profile of a progesterone drug formulation of the present invention.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

It has now been discovered by the inventors that it is possible for hydrophobic active agents to be combined at a high agent loading (that is, in an amount of 50 wt% or greater) with a particular surfactant, polyoxyethylene 40 stearate, and also with a disintegrant. This high loading provides the advantage of obtaining a maximum amount of agent in a minimum amount of carrier to give fluid-activated delivery devices of a small size that are

convenient for use as implants or oral dosage forms. The combination surprisingly maintains the hydrophobic active agent formulation in a non-aggregated form when the formulation is exposed to the fluid environment of use, which provides controlled and uniform release of the agent, and this in turn results in the alleviation of erratic release profiles and system malfunction.

The term "active agent" as used herein describes any beneficial agent or compound that can be delivered by a device according to this invention to produce a beneficial or useful, including a therapeutic, result. The term includes medicines or drugs, such as inorganic or organic drugs, biocides, sterilization agents, food supplements, nutrients, vitamins, sex sterilants, fertility inhibitors and fertility promoters. The agents include drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autocrine systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, polypeptides, steroids, analgesics, local anesthetics, antibiotic agents, anti-inflammatory corticosteroids, ocular drugs and synthetic analogs of these species.

The active agents included in the present invention are hydrophobic, that is they are insoluble or only slightly soluble in water. Any hydrophobic active agent which falls within this definition can be used in the present invention. Such active agents are known in the art or they can be determined without undue experimentation by reference to, for example, *The Merck Index* or *The Physician's Desk Reference* or other similar

pharmaceutical or chemical reference books. Presently preferred hydrophobic active agents for use in this invention are progesterone, phenytoin, and gemfibrozil.

It is to be understood that more than one hydrophobic active agent
5 may be incorporated into the active agent formulation of this invention, and that the use of the term "agent" in no way excludes the use of two or more such active agents. The terms "active agent" and "drug" are used interchangeably herein.

The active agent can be present in this invention in a wide variety of
10 chemical and physical forms, such as uncharged molecules, molecular complexes, and pharmaceutically acceptable acid addition and base addition salts. Derivatives such as esters, ethers and amides can be used. The amount of active agent or drug present in a device according to the invention generally can be from about 0.05 ng to 10 g or more. The devices of the
15 invention generally dispense from 0.1 to 200 mg/hr.

The hydrophobic active agent is present in the invention in a therapeutically effective amount; that is, in an amount that is necessary to provide a desired therapeutic, usually beneficial effect. The active agent will be present in the agent formulation at a loading of 50-99 wt%, preferably at
20 least 60 wt%, and can be in an amount of 85 wt% or greater.

Surprisingly, it has now been found that when a hydrophobic active agent in an amount of at least 50 wt% is combined with a particular surfactant, polyoxyethylene 40 stearate, and also with a disintegrant, that the hydrophobic agent formulation does not aggregate when exposed to a fluid
25 environment, such as an animal body. As a result, the functioning of the delivery system and the delivery of the active agent is greatly improved, providing a continuous and non-erratic agent release profile.

The amount of polyoxyethylene 40 stearate (MYRJ® 52-S, ICI Americas, Inc.) in the formulation of the present invention will be from about 1 wt% to about 25 wt%, preferably from about 3 wt% to about 20 wt%.

The disintegrant for use in the present invention is selected from any
5 natural chemical entities or their derivatives or any synthetic chemicals that can promote rapid disintegration of a solid hydrophobic dosage form. Disintegrants useful herein include, but are not limited to, crospovidone (cross-linked polyvinylpyrrolidone), croscarmellulose sodium (Ac-Di-Sol®, FMC Corporation), sodium starch glycolate (Explotab®, Edward Mendell
10 Co.), alginates, kappa-carrageenan, soya polysaccharides, cross-linked gelatin, ion-exchange resins, cyclodextrin polymers, cross-linked casein, and low substituted hydroxypropylcellulose. Presently preferred disintegrants for use in this invention are crospovidone and croscarmellulose sodium. The disintegrant is present in an amount of from about 5 wt% to about 30 wt%,
15 preferably from about 8 wt% to about 20 wt%.

While the above surfactant and disintegrants are known in the art, it has not previously been known to use these two specific ingredients together in combination with a hydrophobic active agent at a high drug loading of at least 50 wt% to provide an improved formulation for avoiding aggregation of
20 the agent to give improved delivery from a fluid-activated delivery device.

The hydrophobic active agent formulation of the present invention may optionally comprise additional inert ingredients, such as fillers, dyes, binders, lubricants, stabilizers, and the like, as are known in the art.

The formulation of the present invention is of particular use in fluid-
25 activated delivery devices for delivering a hydrophobic active agent to a fluid environment of use, such as the body of an animal. Fluid-activated delivery devices are generally known in the art. The present invention is directed to

an improved delivery device which includes a housing defining an internal compartment, a hydrophobic active agent formulation in the compartment, exit means in the housing for delivering the active agent formulation from the delivery device, a fluid-activated expandable driving member in the
5 compartment, optionally a partition layer between the active agent formulation and the driving member, and optionally a lubricant subcoat; wherein the improvement comprises an active agent formulation comprising a hydrophobic active agent in an amount of 50 wt% or greater, polyoxyethylene 40 stearate, and a disintegrant.

10 FIG. 1 illustrates one embodiment of a delivery device according to the invention. In the following discussion, like reference numerals refer to like elements in the Figures, which Figures are not drawn to scale. In FIG. 1, device 10 comprises a rigid semipermeable housing 12 in the shape of a capsule which surrounds an internal compartment 14. Semipermeable
15 materials useful as housing 12 are known in the art, examples of which are discussed in U.S. Pat. No. 4,874,388, the entire disclosure of which is incorporated herein by reference.

An active agent formulation 15 according to the present invention is present in one portion of compartment 14, formulation 15 comprising a
20 hydrophobic active agent in an amount of at least 50 wt%, the surfactant polyoxyethylene 40 stearate, and a disintegrant. Exit port 13 is present in that portion of housing 12 that is adjacent to the active agent formulation 15 for providing a passageway between internal compartment 14 and the external environment.

25 Device 10 includes a driving member 16 that is fluid-activated. Many different types of fluid-activated driving components are known in the art, examples of which are discussed in detail in U.S. Pat. No. 4,874,388, incorporated previously herein by reference, and may include a water-

swellable composition, an osmotically effective solute, an elementary osmotic pump or a gas-generating composition, for example. A moveable inert partition layer (not shown) may optionally be present to separate the active agent formulation **15** from the driving member **16**, and in a preferred embodiment the partition is substantially impermeable to the passage of fluid.

Device **10** optionally includes a subcoat **18** which is water-soluble and dissolves in the fluid environment of use. Subcoat **18** is not essential to the invention but when it is present, in its hydrated state it provides lubricant means for assisting the active agent formulation **15** to move within compartment **14** towards and out of the exit port **13** as a result of the expanding action of driving member **16**. Lubricant subcoat **18** may be chosen from water-soluble, hydratable materials such as gelatin, commercial materials having gelatin as one component, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and their derivatives, and the like.

FIG. 2 illustrates another embodiment of the present invention. Device **20** comprises a semipermeable wall **12**, an exit port **13**, an internal compartment **14**, and a fluid-activated driving member **16**. Device **20** has a hydrophobic active agent formulation according to the invention, the formulation being present as three tablets **15a**, **15b**, and **15c**. This configuration is merely illustrative, and the device may have agent tablets of a number other than the number shown in FIG. 2.

Device **20** has a lubricant subcoat **18** which initially consists of two parts, a body portion **18a** and a cap portion **18b** to form a capsule. Capsule **18** is useful in the manufacture of device **20** for initially accepting and containing active agent formulation tablets **15a**, **15b**, and **15c** and driving member **16** prior to addition of the semipermeable housing **12**. When device

20 is placed in a fluid environment, capsule 18 hydrates to form a continuous lubricant subcoat.

While FIGS. 1 and 2 illustrate various delivery devices according to the present invention, it is to be understood that these dosage forms are not to be construed as limiting the invention, as the delivery device can take
5 other shapes, sizes and forms for delivering the hydrophobic active agent formulation of the invention to a biological environment of use. The delivery device may be used to deliver a hydrophobic active agent to animals including warm-blooded animals, mammals and humans. The delivery
10 device can be used in hospitals, clinics, nursing homes, veterinary clinics, farms, zoos, laboratories, and other fluid environments of use. The presently preferred environment of use comprises the gastrointestinal tract of a human. However, the devices are not restricted to such use. The environment of use can comprise a body cavity such as the peritoneum, vagina, or rumen
15 (where a density element is then utilized for maintaining the device in the rumen). The device may also be utilized as a subcutaneous implant. A single dispensing device or several dispensing devices can be administered to a subject during a therapeutic program.

EXAMPLE 1

20 A drug delivery device corresponding to the device in FIG. 2 was manufactured for dispensing gemfibrozil to the gastrointestinal tract, as follows.

A drug-layer formulation having a composition of 85.0 wt% gemfibrozil, 8.0 wt% croscarmellulose sodium (Ac-Di-Sol®, FMC
25 Corporation), 3.0 wt% polyoxyethylene 40 stearate (MYRJ® 52-S), 3.0 wt% hydroxypropylmethylcellulose (HPMC E5), 0.5 wt% colloidal silicon dioxide and 0.5 wt% magnesium stearate was prepared by first passing each of the

first four ingredients through a 40-mesh screen and then blending them together. Ethanol was slowly added into the blend and mixed with the blend until even consistency of a wet mass was attained. The wet mass was passed through a screen and then dried in an oven. Then, the silicon
5 dioxide and magnesium stearate were added to the granules and blended. The drug-layer granules were compressed into single-layer flat-flat tablets each weighing 212 mg and flat-round tablets each weighing 282 mg, using a press with a 17/64-inch round punch.

An osmotic driving member tablet having a composition of 58.75 wt%
10 sodium carboxymethylcellulose (7H4F), 30.0 wt% sodium chloride, 5.0 wt% HPMC E5, 1.0 wt% red ferric oxide, 5.0 wt% hydroxypropylcellulose (EF) and 0.25 wt% magnesium stearate was prepared by first passing each of the first four ingredients through a 40-mesh screen and then blending them together in a fluid-bed granulator and spraying the blend with the
15 hydroxypropylcellulose in solution in purified water until homogeneous granules formed. These granules were passed through an 8-mesh screen and mixed with the magnesium stearate. The osmotic granules were compressed into single-layer flat-round tablets each weighing 250 mg, using a press with a 17/64-inch round punch.

20 To assemble the device, one osmotic tablet was placed in the bottom of one piece of a two-piece size "0" elongated gelatin capsule. Two flat-flat drug-layer tablets were placed in the capsule on top of the osmotic tablet. One flat-round drug-layer tablet was placed in the bottom of the other portion of the gelatin capsule and the two capsule pieces were fitted tightly together.
25 The capsule was then coated with a semipermeable wall, the wall composition comprising 75.0 wt% cellulose acetate, having an acetyl content of 39.8%, and 25.0 wt% polyethylene glycol, having a molecular weight of 3,350. The wall-forming composition was dissolved in acetone/methanol (80/20, wt/wt) mixed solvent to make a 4% solid solution. The wall

composition was sprayed onto the capsule to give a membrane weight of about 100 mg. Finally, an exit orifice (155 mil or 190 mil) was cut mechanically through the semipermeable membrane wall on the drug-layer end of the capsule. The residual solvent was removed by drying the device
5 at 30°C and 50% humidity for 3 days.

The devices were tested for release characteristics by placing them in artificial intestinal fluid (AIF). They were removed and placed in new AIF at hourly intervals and the previous fluid was tested for the presence of gemfibrozil. The devices were found to deliver gemfibrozil at an average
10 rate of 90.0 mg/hr with 90% of the drug released in 6 hrs.

EXAMPLE 2

Following the procedures of Example 1, a gemfibrozil device was prepared having the following composition.

~~-----~~ The gemfibrozil formulation was 66.7 wt% gemfibrozil, 0.5 wt%
15 magnesium stearate, 5.0 wt% MYRJ 52-S, 10.0 wt% Ac-Di-Sol, 12.8 wt% sodium phosphate and 5.0 wt% HPMC E-5. The final weight of the gemfibrozil formulation in the device was 600 mg.

The osmotic driving member composition was 58.5 wt% sodium carboxymethyl cellulose 7H4F, 35.0 wt% sodium chloride, 6.0 wt% HPMC E-
20 5, 0.25 wt% ferric oxide and 0.25 wt% magnesium stearate. The final weight of the composition in the device was 300 mg.

The semipermeable membrane wall was 70.0 wt% cellulose acetate 398-10 (39.8% acetyl content) and 30.0 wt% polyvinyl pyrrolidone (PVP K29-32). The final weight of the membrane wall was 74.6 mg. The exit orifice
25 was 190 mils.

These devices were tested for gemfibrozil release in artificial gastric fluid (AGF), following the procedures of Example 1. The release rate profile is shown in FIG. 3A (n=4).

For comparison purposes, a device having a prior art gemfibrozil formulation, without MYRJ 52-S or croscarmellulose, was prepared, the composition of the gemfibrozil formulation being 66.7 wt% gemfibrozil, 0.5 wt% magnesium stearate, 27.8 wt% sodium phosphate, and 5.0 wt% HPMC 5-E. The devices were tested for gemfibrozil release, as above, and the release rate profile is shown in FIG. 3B (n=4).

EXAMPLE 3

Following the procedures of Example 1, gemfibrozil-containing devices were prepared having the formulations under Table A:

TABLE A							
	Gemfibrozil	Mg Stearate	MYRJ	Ac-Di-Sol	Na ₂ PO ₃	HPMC	N80 Polyox
Device A (Ex. 2)	66.7	0.5	5.0	10.0	12.8	5.0	—
Device B	66.7	0.5	—	10.0	7.8	5.0	10.0
Device C	66.7	0.5	5.0	—	12.8	5.0	10.0
Device D	66.7	0.5	—	—	17.8	5.0	10.0

For comparison purposes, the devices were tested for gemfibrozil release against the gemfibrozil device of Example 2, in AGF. The release rate profiles are shown in FIG. 4A (formulation A, having surfactant and

disintegrant; same graph as in FIG. 3A; n=4), FIG. 4B (formulation B, no surfactant; n=3), FIG. 4C (formulation C, no disintegrant; n=4) and FIG. 4D (formulation D, no surfactant or disintegrant; n=4).

EXAMPLE 4

- 5 Following the procedures of Example 1, gemfibrozil-containing devices were prepared having the formulations under Table B:

TABLE B						
	Gemfibrozil	Mg Stearate	MYRJ	Ac-Di-Sol	HPMC	N10 Polyox
Device A	66.7	0.5	5.0	12.8	5.0	10.0
Device B	66.7	0.5	—	12.1	5.0	15.7

- 10 For comparison purposes, the devices were tested for gemfibrozil release in AGF. The release rate profiles are shown in FIG. 5A (formulation A, having surfactant and disintegrant; n=3) and FIG. 4B (formulation B, no surfactant; n=3).

EXAMPLE 5

- 15 A phenytoin-containing device according to the present invention and corresponding to the device of FIG. 1 was prepared, generally following the procedures of Example 1.

- The composition of the phenytoin drug tablet was 60.0 wt% phenytoin, 16.0 wt% sorbitol, 10.0 wt% MYRF 52-S, 10.0 wt% Ac-Di-Sol, 1.5 wt%
20 magnesium stearate and 2.5 wt% PVP K29-32. The phenytoin composition

was pressed into a single-layer elongated flat-round tablet weighing 460.0 mg.

The composition of the osmotic driving member tablet was the same as in Example 1. The final weight of the driving member in the device was
5 184.0 mg.

To assemble the device, 460 mg of the above phenytoin formulation and 184 mg of the osmotic composition were pressed together to form a bilayer capsule, using either a laboratory Carver press or a vertical compressing machine. A lubricant laminate subcoat of 95.0 wt% Natrosol
10 and 5.0 wt% PEG 3350 was then spray-coated onto the bilayer drug/osmotic capsule. The laminate-coated capsule was dried and then coated with an outer semipermeable wall. The semipermeable membrane composition was 85.0 wt% cellulose acetate 398-10 and 15.0 wt% PEG 3350. The final weight of the membrane encasing the device was 49.0 mg. An exit orifice of
15 190 mils was then cut into the wall at the drug end of the capsule.

These devices were tested for phenytoin release in AIF, following the procedures of Example 1. The release rate profile is shown in FIG. 6 (n=5).

EXAMPLE 6

A progesterone-containing device according to the present invention
20 was prepared, generally following the procedures of Example 1 and corresponding to the device of FIG. 1.

The composition of the progesterone drug tablets were 60.0 wt% progesterone, 9.5 wt% polyethylene oxide (Polyox® N10), 12.0 wt% MYRJ 52-S, 15.0 wt% cross-linked polyvinylpyrrolidone (XL-10; crospovidone), 0.5
25 wt% magnesium stearate and 3.0 wt% HPMC E-5.

The composition of the osmotic driving member tablet was the same as in Example 1.

To assemble the device, following the procedures of Example 4, 500 mg of the above progesterone formulation and 250 mg of the osmotic composition were compressed together to form a bilayer capsule-shaped tablet. A lubricant laminate subcoat (43.4 mg) of 95.0 wt% Natrosol and 5.0 wt% PEG 3350 was coated onto the drug/osmotic bilayer capsule prior to coating with the semipermeable membrane. The semipermeable membrane composition was 90.0 wt% cellulose acetate 398-10 and 10.0 wt% PEG 3350. The final weight of the membrane encasing the device was 85.0 mg. The exit orifice was 190 mils.

These devices were tested for progesterone release in AIF, following the procedures of Example 1. The release rate profile is shown in FIG. 7 (n=3).

15

EXAMPLE 7

A gemfibrozil-containing device was prepared following the procedures of Example 1. The drug-layer and osmotic-layer compositions of the device were the same as those in Example 1. The semipermeable wall composition was 85.0 wt% cellulose acetate 398-10 and 15.0 wt% PEG 3350, and weighed 125 mg.

The devices were tested for gemfibrozil release in AIF, and they delivered the drug at an average rate of 30 mg/hr, with 90% of the drug released in 18 hrs.

EXAMPLE 8

A different gemfibrozil-containing device was prepared following the procedures of Example 1. The composition of the osmotic layer is identical to that in Example 1, and the osmotic tablet weighed 300 mg. The
5 semipermeable wall membrane composition was also identical to that of Example 6 and weighed 150 mg in the device of this example.

The gemfibrozil drug-layer formulation had a composition of 66.7 wt% gemfibrozil, 14.3 wt% croscarmellulose sodium, 5.0 wt% polyoxyethylene 40 stearate, 9.5 wt% polyethylene oxide (Polyox N10), 3.0 wt% HPMC 35, 1.0
10 wt% colloidal silicon dioxide, and 0.5 wt% magnesium stearate. The drug formulation in the device of this example was composed of one flat-round tablet and two flat-flat tablets, each weighing 133 mg.

The devices were tested for gemfibrozil release in AIF, and they delivered the drug at an average rate of 20 mg/hr, with 90% of the drug
15 released in 18 hrs.

EXAMPLE 9

A progesterone-containing device according to the present invention was prepared, following the procedures of Example 1.

The composition of the progesterone drug tablets were 60.0 wt%
20 progesterone, 16.5 wt% MYRJ 52-S, 20.0 wt% Aci-Di-Sol, 3.0 wt% HPMC E-5 and 0.5 wt% magnesium stearate. The total weight of the drug tablets in the device was 500 mg.

The composition of the osmotic driving member tablet was the same as in Example 1. The weight of the driving member in the device was 250 mg.

To assemble the device, one osmotic tablet and two drug tablets (one
5 flat-flat tablet weighing 220 mg and one flat-round tablet weighing 280 mg)
were placed in a "0"-sized gelatin capsule. The capsule was coated with a
semipermeable wall membrane composition identical to that of Example 6
and weighing 100 mg in the device of this example.

The devices were tested for progesterone release in AIF, and they
10 delivery the drug at an average rate of 13.5 mg/hr with 90% of the drug
released in 20 hr.

WHAT IS CLAIMED IS:

1. A hydrophobic active agent formulation comprising:
50-99 wt% of a hydrophobic active agent;
1-25 wt% of polyoxyethylene 40 stearate; and
5 5-30 wt% of a disintegrant, selected from those disintegrants
that promote rapid disintegration of a solid hydrophobic dosage form.
2. A formulation according to Claim 1 wherein the hydrophobic
active agent is selected from the group consisting of gemfibrozil, phenytoin
and progesterone.
- 10 3. A formulation according to claim 1 wherein the disintegrant is
selected from croscarmellulose sodium and crospovidone.
4. A formulation according to claim 1 wherein the hydrophobic
active agent is gemfibrozil and the disintegrant is croscarmellulose sodium.
- 15 5. A formulation according to claim 1 wherein the hydrophobic
active agent is phenytoin and the disintegrant is croscarmellulose sodium.
6. A formulation according to claim 1 wherein the hydrophobic
active agent is progesterone and the disintegrant is selected from
croscarmellulose sodium and crospovidone.
- 20 7. A formulation according to claim 1 which comprises at least 60
wt% hydrophobic active agent, 3-20 wt% polyoxyethylene 40 stearate, and
8-20 wt% disintegrant.
8. A formulation according to claim 7 wherein the disintegrant is
selected from croscarmellulose sodium and crospovidone.

9. An improved delivery device for dispensing a hydrophobic active agent to a fluid environment of use, the delivery device comprising a housing defining an internal compartment, a hydrophobic active agent formulation in the compartment, exit means in the housing for delivering the active agent formulation from the delivery device, and a fluid-activated driving member in the compartment; wherein the improvement comprises an active agent formulation comprising 50-99 wt% of a hydrophobic active agent, 1-25 wt% of polyoxyethylene 40 stearate, and 5-30 wt% of a disintegrant selected from those disintegrants that promote rapid disintegration of a solid hydrophobic dosage form.

10. An improved delivery device according to claim 9 wherein the disintegrant is selected from croscarmellulose sodium and crospovidone.

11. An improved delivery device according to claim 9 wherein the hydrophobic active agent is selected from the group consisting of gemfibrozil, phenytoin and progesterone.

12. An improved delivery device according to claim 9 wherein the hydrophobic active agent is gemfibrozil and the disintegrant is croscarmellulose sodium.

13. An improved delivery device according to claim 9 wherein the hydrophobic active agent is phenytoin and the disintegrant is croscarmellulose sodium.

14. An improved delivery device according to claim 9 wherein the hydrophobic active agent is progesterone and the disintegrant is selected from croscarmellulose sodium and crospovidone.

15. An improved delivery device according to claim 9 which comprises at least 60 wt% hydrophobic active agent, 3-20 wt% polyoxyethylene 40 stearate, and 8-20 wt% disintegrant.

16. An improved delivery device according to claim 15 wherein the
5 disintegrant is selected from croscarmellulose sodium and crospovidone.

17. An improved delivery device according to claim 9 which further comprises a partition layer between the active agent formulation and the driving member.

18. An improved delivery device according to claim 9 which further
10 comprises a lubricant subcoat.

1/4

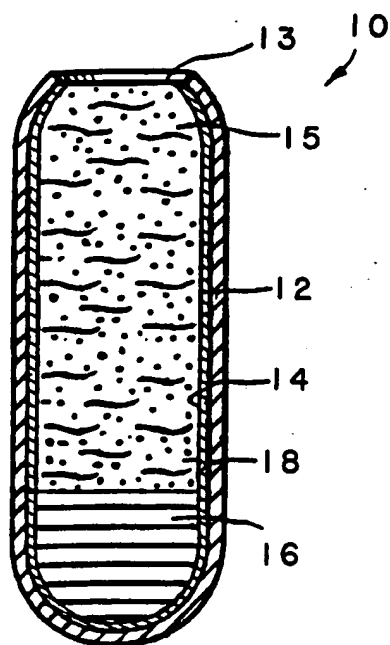


FIG. 1

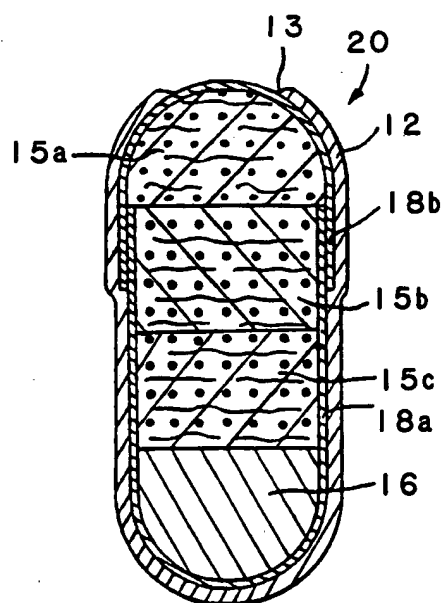


FIG. 2

2 / 4

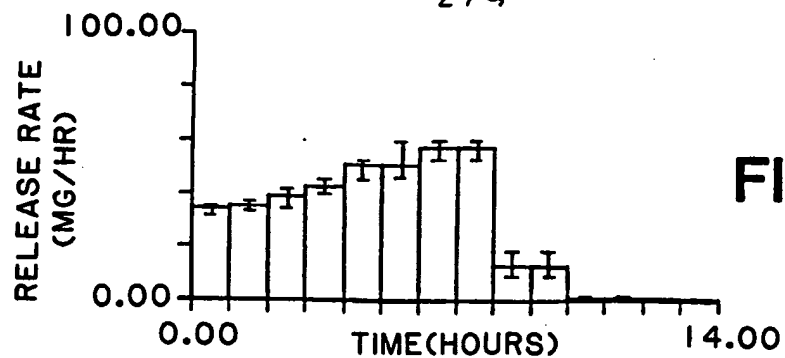


FIG. 3A

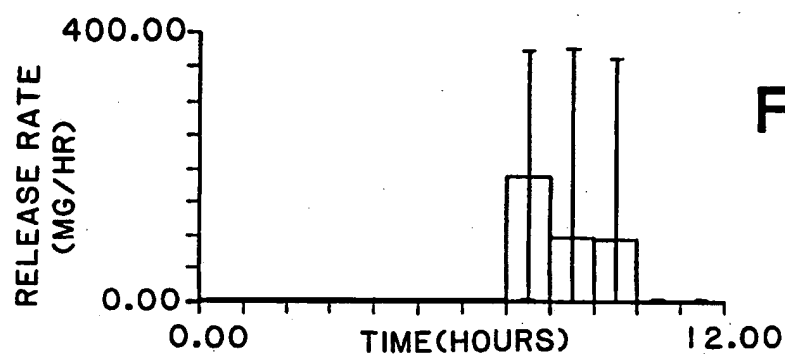


FIG. 3B

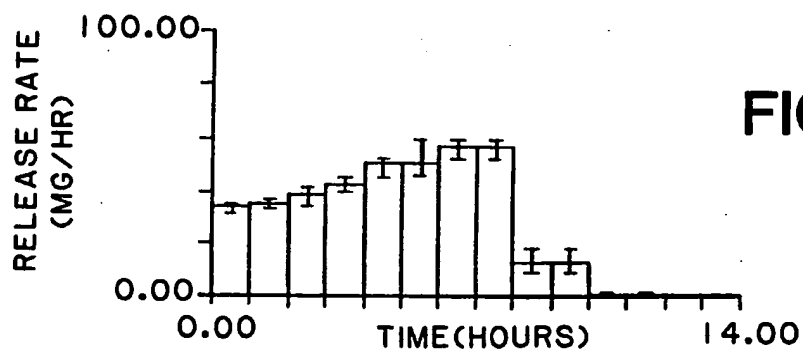


FIG. 4A

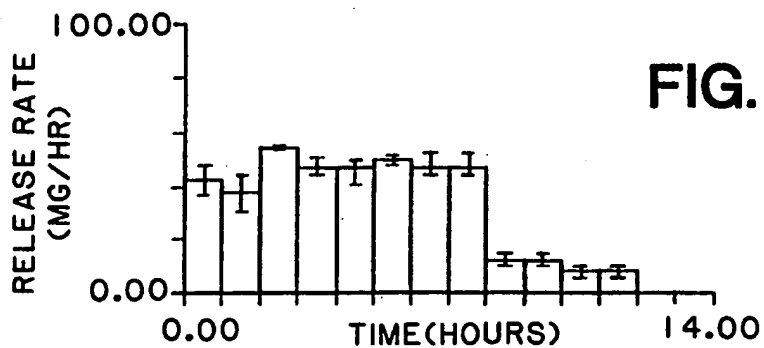
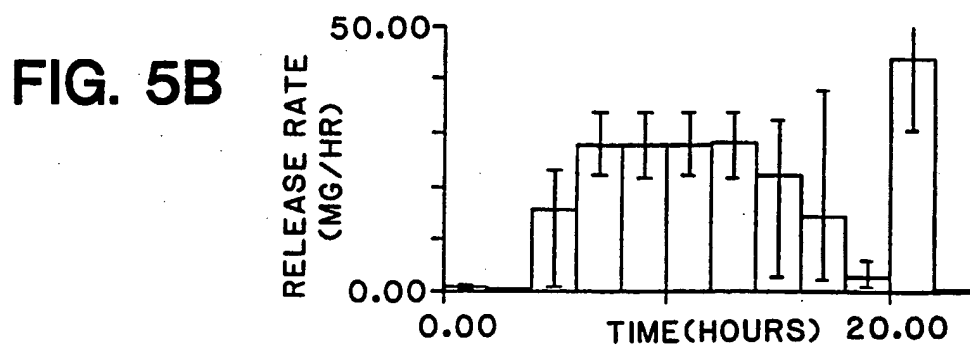
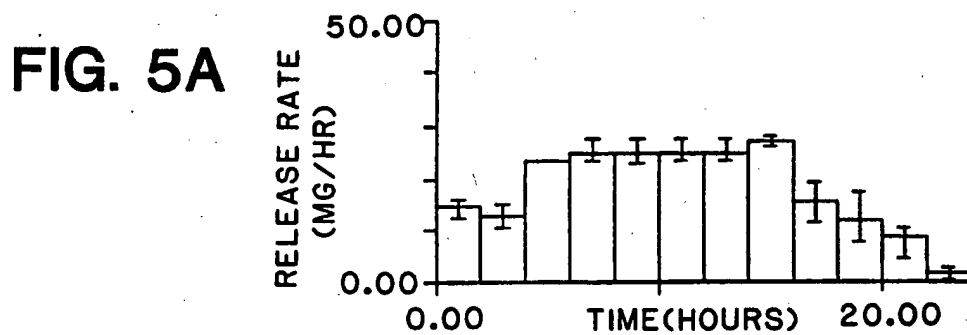
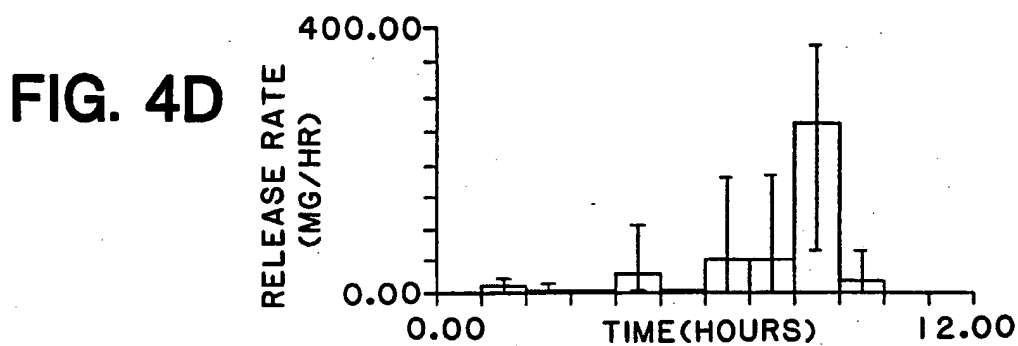
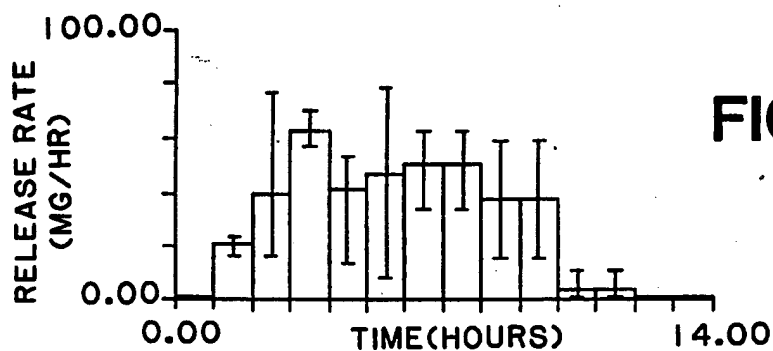


FIG. 4B

3/4



4 / 4

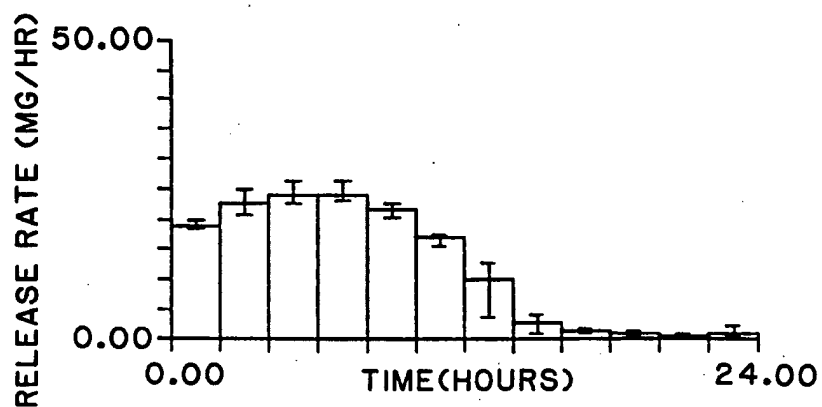


FIG. 6

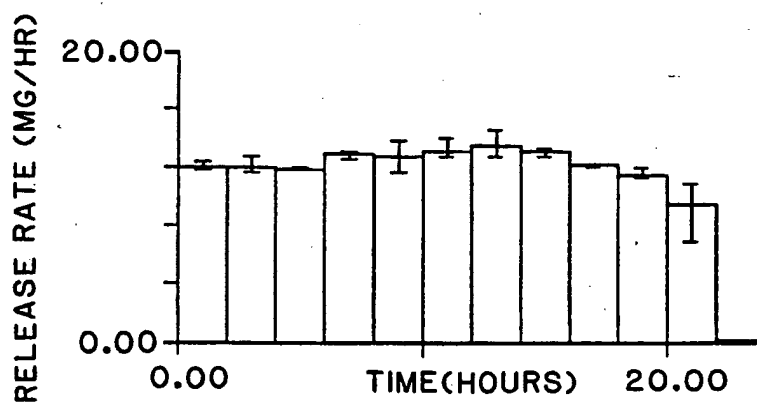


FIG. 7

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/US 94/09709

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 100, no. 24, 11 June 1984, Columbus, Ohio, US; abstract no. 197699, HIRAKAWA, YOSHIYUKI, ET AL. 'Studies on development of the ultrafine size reduction method of slightly soluble medicinal crystals. V. Size reduction of phenytoin and phenobarbital' & YAKUGAKU ZASSHI, vol.104, no.1, 1984 pages 91 - 96	1,2,7,9, 11,15,17
Y	US,A,5 192 550 (DAVID E. EDGREN ET AL.) 9 March 1993 -see claims 1,2 see figure 2 see column 5, line 33 - column 6, line 22	1,2,7,9, 11,15,17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 December 1994

Date of mailing of the international search report

06.01.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/US 94/09709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5192550	09-03-93	US-A- 5190763	02-03-93
		US-A- 5221536	22-06-93
		AT-T- 113203	15-11-94
		AU-B- 641770	30-09-93
		AU-A- 7854391	27-11-91
		DE-D- 69104830	01-12-94
		EP-A- 0527835	24-02-93
		WO-A- 9116885	14-11-91

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☒ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.